The Effect of Consolidation Chemotherapy for LA-NSCLC Patients Receiving Concurrent Chemoradiotherapy

Eş Zamanlı Kemoradyoterapi Alan Lokal İleri KHDAK Hastalarda Konsolidasyon Kemoterapisinin Etkinliği

Consolidation Chemotherapy for LA-NSCLC

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Özet

Amaç: Lokal ileri evre küçük hücreli dışı akciğer kanserinde (KHDAK) eşzamanlı kemoradyoterapi (EKRT) sonrası uygulanan konsolidasyon kemoterapisinin etkinliği ve güvenilirliği yeterince aydınlatılmamıştır. Bu nedenle çalışmamızda konsolidasyon kemoterapisinin etkinliğini ve güvenliliğini araştırmayı amaçladık. Gereç ve Yöntem: EKRT sonrası konsolidasyon KT alan (n:20) ve almayan (n:63) 83 Lokal ileri evre KHDAK'lu hastanın progresyonsuz ve total sağkalım süreleri retrospektif olarak değerlendirildi. Tüm hastaların tanıları sito-histolojik olarak kanıtlı idi ve 2009 American Joint Committee on Cancer evreleme sistemine göre klinik evreleri Evre III idi (n:48 IIIA, n:35 IIIB sırasıyla).Tüm hastalar küratiftorakal radyoterapiyle eşzamanlı platin bazlı ikili kemoterapi aldı. Bulgular: Olguların ortalama yaşı 59 (±7.3) idi, %89.2'i (n:74) erkek iken yalnızca 9 hasta kadındı (%10.8). EKRT sonrası konsolidasyon KT alan grup (10.4 ay) almayana göre (13.8 ay)log-rank analizde istatistiksel anlamlı daha kısa progresyonsuz sağkalıma sahipti (p=0.046). İki grup arasında genel sağkalım açısından istatistiksel anlamlı bir fark saptanmadı (17.4 ay, 21 ay sırasıyla) (p>0.05). Konsolidasyon KT alan grupta istatistiksel anlamlı daha sık hematolojik toksisite gözlendi (p<0.001). Tartışma: Çalışmamızda lokal ileri evre KHDAK'lu hastalarda eşzamanlı kemoradyoterapi sonrası uygulanan konsolidasyon kemoterapisinin genel sağkalımı arttırmadığı bununla birlikte daha sık hematolojik toksisiteye neden olduğu gözlenmiştir.

Anahtar Kelimeler

Küçük Hücreli Dışı Akciğer Kanseri; Eşzamanlı Kemoradyoterapi; Konsolidasyon Kemoterapisi

Abstract

Aim: The efficacy and safety of consolidation chemotherapy (CCT) following concurrent chemoradiotherapy are not adequately established for patients with locally advanced non-small-cell lung cancer (LA-NSCLC). In this context, the present study aims to evaluate the efficacy and toxicity of CCT. Material and Method: We retrospectively analyzed the overall survival (OS) and progression-free survival (PFS) of 83 LA-NSCLC patients treated with concurrent CRT as an initial treatment with (n:20) or without CCT (n:63). All patients were cytohistologically proven to have NSCLC and diagnosed with clinical Stage III (n:48 for IIIA and n:35 for IIIB) according to the staging system published by the American Joint Committee on Cancer (AJCC) in 2009. All patients received curative thoracic radiotherapy with concurrent platinum doublet chemotherapy. Results: The mean age of the lung cancer patients was 59 (±7.3); 89.2% were male (n:74),and there were only 9 female patients (10.8%).When we compared the outcome of LA-NSCLC patients treated with CCT (median 10.4 months) to the patients treated without CCT (median 13.8 months), the log-rank analysis demonstrated a statistically significant difference for an inferior progression-free survival (p=0.046) in patients receiving CCT. However, no significant association was observed for overall survival (17.4, 21 months, respectively) (p>0.05). Patients with CCT presented higher levels of hematological side effects compared with the patients without CCT (p<0.001). Discussion: The present study showed that consolidation chemotherapy (CCT) following concurrent chemoradiotherapy did not prolong the overall survival but caused higher levels of chemotherapy-related hematological toxicity in the case of LA-NSCLC.

Keywords

Non-Small-Cell Lung Cancer; Concurrent Chemoradiotherapy; Consolidation Chemotherapy

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Introduction

Lung cancer remains the primary cause of cancer-related deaths worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases, and at the time of diagnosis, nearly 40% of patients with NSCLC present locally advanced non-small-cell lung cancer (LA-NSCLC) (unresectable Stage III disease) [2]. The standard treatment for LA-NSCLC consists of concurrent platinum-based chemotherapy and thoracic radiotherapy [3-6]. This treatment yields superior survival results compared with exclusive radiotherapy or sequential chemoradiotherapy (CRT) [7].

Various studies have explored the efficacy of consolidation chemotherapy, i.e. repetitive cycles of treatment through the immediate postremission period (CCT) following a concurrent CRT. However, those studies report discordant results. The Southwest Oncology Group had treated patients with concurrent CRT followed by a consolidation docetaxel monotherapy and achieved a promising median survival of 26 months [8]. A retrospective analysis of 203 cases showed that CCT might prolong survival compared with exclusive CRT for LA-NSCLC, especially for males, patients < 60 years of age, with non-squamous histology, pre-treatment KPS ≥ 80, Stage IIIB, stable disease, and radiotherapy dose ≥ 60 Gy [9]. In contrast, a recent pooled analysis of 45 studies on CCT revealed no survival benefit for the LA-NSCLC patients [2]. However, a subgroup analysis demonstrated that some populations (mostly from Japan and Korea) tended to benefit from CCT, but results were not statistically significant [2].

For patients with LA-NSCLC, the efficacy and safety of consolidation chemotherapy following concurrent chemoradiotherapy have not been adequately established. The present study thus aims to evaluate the efficacy and toxicity of CCT in this context.

Material and Method

We retrospectively analyzed the clinical records of LA-NSCLC patients treated with concurrent CRT as an initial treatment at our Chest Diseases Hospital from January 2010 to January 2014. All patients were cytohistologically proven to have NSCLC and diagnosed with clinical Stage III according to the staging system published by the American Joint Committee on Cancer (AJCC) in 2009. All of them received curative thoracic radiotherapy with concurrent platinum doublet chemotherapy. Responses to treatment were evaluated one month after the completion of the concurrent CRT. Treatment responses were classified as complete response (CR), partial response (PR), and stable disease (SD) according to the Response Evaluation Criteria for Solid Tumors (RECIST version 1.1). Treatment toxicities were graded based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4 (http://evs.nci.nih.gov/ftp1/CTCAE). This retrospective study was approved by the ethics committee of our hospital.

Concurrent Chemoradiotherapy

Radiotherapy (RT) was delivered using conventional fractionation (1.8 Gy/day, 5 days/week) with a total dose of 54-66 Gy and applying 6-18 MV photon beams. All patients received a three-dimensional conformal RT. The gross tumor volume (GTV) consisted of the primary tumor and the regional lymph nodes considered positive (SUVmax>2.5) on positron emission tomography (PET) scan even if not involved according to computed tomography (CT) scan. For an identification of GTV on CT, pulmonary window settings were used to contour the pulmonary tumor and hilum, and the predefined mediastinal window settings were employed to contour the mediastinal lesions. Margins for GTV to the clinical target volume (CTV) were 5-7 mm for squamous cell carcinoma (SCC) and 6-8 mm for other histological types. In order to generate the planning target volume (PTV), a 5-10 mm margin was added to the CTV to compensate for setup errors and target motion. The thoracic radiotherapy (TRT) was delivered to this volume at a daily dose of 1.8-2.0 Gy, for a total dose of 45-46 Gy over 5 weeks. At weeks 6 and 7, TRT was delivered to a smaller target volume including the primary tumor and lymph nodes known to be involved with the disease.

Dose volume histograms for the PTV, normal lung, spinal cord, esophagus, and heart have been calculated to gain full knowledge of the three dimensional dose distribution. Coverage of the CTV by the 95% isodose line was mandatory. PTV coverage with 95% isodose line could not be achieved in some patients due to critical organ dose constraints. The treatment was delivered using a linear accelerator.

Consolidation Chemotherapy

Those patients treated with consolidation chemotherapy received either platinum-based or single-agent therapy. Blood cell counts and blood chemistry examinations were performed once a week through the concurrent CRT period. The follow-up evaluations consisted of a physical examination, complete blood cell counts, serum biochemistry, thoracic CT scans, and other necessary imaging examinations where indicated. The clinical and imaging examinations were performed at intervals of 3 months for the first year, then every 6 months for the following 2 years, and annually thereafter. Local recurrence was defined as primary tumor recurrence and regional recurrence was defined as a new N3 or recurrence in the mediastinum, hilum, and/or supraclavicular fossa. Distant metastases were specified as contralateral lung and metastatic extrathoracic lymph nodes or any other organ metastasis. Disease progression was determined based on a radiologic or histologic examination.

Statistical Analysis

We entered the research data into a database created using the SPSS (Statistical Package for Social Sciences) Windows version 15.0 and used the same software to conduct a statistical analysis of the data. Descriptive statistics summarized frequencies and percentages for categorical variables, and mean and standard deviation for continuous variables. Patients' demographic characteristics were presented. Groups with and without chemotherapy treatment were reshuffled with qualitative variables in order to obtain frequencies and percentiles, and differences between the groups were compared through chi-square test methods. We took the overall survival (OS) to start from the beginning of concurrent CRT to the time of death or last follow-up. Progression-free survival (PFS) was defined as the time from the beginning of concurrent CRT to the time of tumor progression or last follow-up. Progression-free and over-

all survival analyses relied on Kaplan-Meier's method of survival analysis, and groups with and without adjuvant chemotherapy were compared through the log-rank test. Type 1 error margin was set at α:0.05 for all tests, to which we applied two-way testing. A value of $p<0.05$ was considered to indicate a statistically significant difference between the groups.

Results

The mean age of patients with lung cancer was 59.8 (± 7.3). Most of them were male (n:74; 89.2%); there were only 9 female patients (10.8%). Forty-eight of 83 patients had ECOG performance status (PS) of 0 and the rest (n:37; 44.6%) had ECOG PS 1. Just over half of them had Stage IIIA (n:48; 57.8%) and the rest had Stage IIIB (n:35; 42.2%) disease. Pathologically, the LA-NSCLC patients were diagnosed with several types of cancer including squamous cell carcinoma, adenocancer, non-small-cell cancer, and others (71.1%; 16.9%; 9.6%; 2.4% respectively).Demographic variables of the patients and their tumor characteristics are presented in Table 1.

Table 1.Demographic variables of the patients and tumor characteristics

	n (%)
Gender	
Male	74 (89.2)
Female	9 (10.8)
Primary Tumor	
T1b	
T2a	
T2b	
T3	13 (15.7)
T4	51 (61.4)
Reginal Lymph Nodes	
N0	10 (12.0)
N1	13 (15.7)
N2	49 (59.0)
N3	11 (13.3)
Stage	
IIIA	48 (57.8)
IIIB	35 (42.2)
ECOG	
0	46 (55.4)
1	37 (44.6)
Pathology	
Squamous	59 (71.1)
Adenocancer	14 (16.9)
Non-small-cell	8 (9.6)
Other	2 (2.4)
Consolidation chemotherapy	
Present	20 (24.1)
Absent	63 (75.9)

Following curative thoracic radiotherapy with concurrent platinum doublet chemotherapy, 20 patients (24.1%) were treated with adjuvant chemotherapy [n:12 for stage IIIA (25%), n:8 for Stage IIIB (22.9%)], and 63 patients (75.9%) received no adjuvant treatment. Twelve patients received platinum doublet treatment and 8 patients were administered single-agent chemotherapy as adjuvant treatment. Taxane plus platinum (n:8) was the most commonly used adjuvant treatment as part of the present study. An evaluation of the post-treatment responses revealed a progression in 29 (34.9%) and regression in 43 (51.9%) patients. Others had stable responses to treatment. During the follow-up, we detected progression in 78.3% of the patients (n:65).Those patients with CCT had higher levels of hematological toxicity compared to the patients without CCT ($p<0.001$). The toxicity of both concurrent chemotherapy and consolidation treatment was hematological. A hematological adverse effect, at any grade, was found in 69.9% and 26.5% of the patients, respectively. Fifty-nine patients (71.1%) had died and 28.9% (n:24) were alive at the time of publication.

Patients' characteristics were analyzed with respect to whether they had received CCT or not; only the patients with hematologic toxicity of chemotherapy ($p<0.0001$) presented statistical significance. As we compared the outcome of LA-NSCLC patients with and without CCT, a log-rank analysis demonstrated a statistically significant difference for a worse progression-free survival ($p=0.046$); however, we did not observe a significant association with overall survival (Figures 1 and 2).

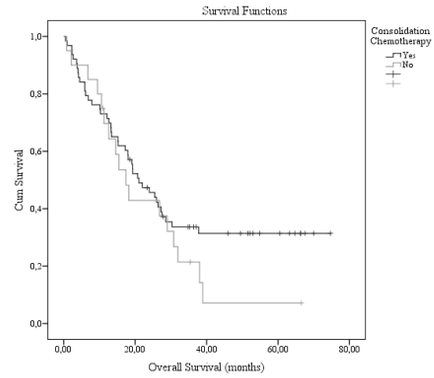

Figure 1. The overall survival curves of the patients with or without consolidation chemotherapy ($p>0.05$)

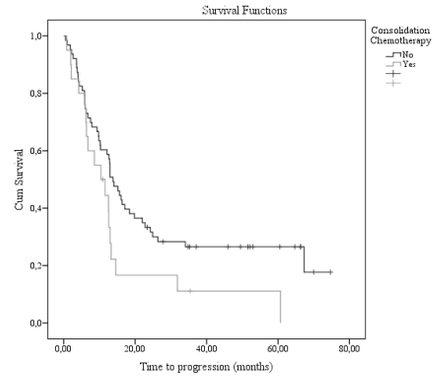

Figure 2. The progression-free survival curves of the patients with or without consolidation chemotherapy ($p=0.046$)

Discussion

In this trial, 83 LA-NSCLC patients with stage IIIA or IIIB initially underwent curative thoracic radiotherapy with concurrent chemotherapy. After CRT, those patients who had received consolidation treatment had inferior PFS vis-à-vis the patients who did not receive any additional chemotherapy. Because of the high rates of local or systemic recurrence in locally advanced

lung cancer, several studies have investigated the additional role of CCT [10]. However, these studies report contradictory results. Also, there is a limited number of studies on the efficacy of CCT after concurrent chemo-RT administered to a large number of patients in a randomized manner.

The contradictory results reported by the aforementioned studies are as follows: There were three randomized trials evaluating the efficacy of CCT for patients with LA-NSCLC, which concluded that addition of CCT did not lead to a significant prolongation of survival [11-13]. A pooled analysis including 41 studies (7 phase III studies and 34 phase II studies) conducted by Kazuyuki et al. did not support the efficacy of consolidation chemotherapy after concurrent chemoradiotherapy in terms of survival outcome for LA-NSCLC patients [2]. They found a median OS of 17.9 months in studies without CCT and 19.0 months in studies including CCT with an HR 0.94. Another multinational randomized trial for 420 patients with LA-NSCLC also provided evidence that the addition of CCT would not yield a significant survival benefit or reduced risk of death [14].Yet, opposite conclusions are available in the literature. In a retrospective analysis of 203 LA-NSCLC patients, Liu et al. found that CCT might prolong survival compared with CRT alone. The benefit was mostly observed in males, patients < 60 years of age, with non-squamous histology, pre-treatment KPS ≥ 80, Stage IIIB, stable disease, and radiotherapy dose ≥ 60 Gy [9]. In a similar Turkish study, Stage IIIB NSCLC patients treated with CRT followed by CCT had a superior outcome in terms of PFS and OS when compared to induction chemotherapy followed by CRT or exclusive chemoradiotherapy groups [15].

There also was not a clearly superior chemotherapy regimen in Stage III LA-NSCLC patients after CRT. Many randomized phase II or III studies were carried out in order to determine the optimal treatment schedule for these group of patients. In inoperable Stage III non-small-cell lung cancer patients, monotherapies for consolidation, such as exclusive docetaxel [8,11,16] or combination regimens, vinorelbine and cisplatin [13,17,18], docetaxel and cisplatin [14,19], bi-weekly docetaxel and carboplatin [20], paclitaxel and carboplatin [21,22], docetaxel plus carboplatin [12,23], compared with best supportive care (or not), were all investigated. None of the specific regimens was determined to be superior to another as the drug regiments were not compared.

In patients with LA-NSCLC, CCT after concurrent chemo-RT may still be used by some clinicians despite the absence of a significant survival benefit in favor of additional chemotherapy. Consolidation therapy with platinum and taxane/vinorelbine combination may have a role in chemotherapy-related toxicity especially in high-risk patients with good performance status for whom recurrence or metastasis is highly likely and for those with a stable disease without progression after chemoradiotherapy.

The last decade has seen great advances in the treatment of metastatic NSCLC patients. Molecular-targeted agents and new immunotherapeutics actually did improve the prognosis of this incurable disease and changed the treatment guidelines fundamentally. These new treatment strategies will continue to be tested for use with LA-NSCLC patients alongside the concurrent chemoradiotherapy and a significant progress in survival may be achieved. Therefore, further clinical trials, including novel treatment agents, will be required to evaluate the feasibility of consolidation treatment, which may increase the rate of cured LA-NSCLC patients.

Competing interests

The authors declare that they have no competing interests.

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